Structure of the N-terminal domain of PEX1 AAA-ATPase

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Peroxisomes are responsible for several pathways in primary metabolism, including beta-oxidation and lipid biosynthesis. PEX1 and PEX6 are hexameric AAA-type ATPases, both of which are indispensable in targeting over 50 peroxisomal resident proteins from the cytosol to the peroxisomes. Although the tandem AAA-ATPase domains in the central region of PEX1 and PEX6 are highly similar, the N-terminal sequences are unique. To better understand the distinct molecular function of these two proteins, we analyzed the unique N-terminal domain (NTD) of PEX1. Extensive computational analysis revealed weak similarity of PEX1 NTD to the N-terminal domains of other membrane related type II AAA-ATPases, such as VCP / p97 and NSF. We have determined the crystal structure of mouse PEX1 NTD at 2.05 Å resolution, which clearly demonstrated that the domain belongs to the double-psi-barrel fold family found in the other AAA-ATPases. The N-domains of both VCP and NSF are structural neighbors of PEX1 NTD with a 2.7 Å and 2.1 Å r.m.s.d. of backbone atoms, respectively. Our finding suggest that the supra-domain architecture, which is composed of a single N-terminal domain followed by tandem AAA domains, is a common feature of organellar membrane-associating AAA-ATPases. We propose that PEX1 functions as a protein unfoldase in peroxisomal biogenesis, using its N-terminal putative adaptor-binding domain.

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